

## REMARKS

Claims 2 through 11 are pending in the application. Claims 1 and 12-17 are cancelled.

The Examiner has objected to the title of the specification. In response thereto, the specification's title has been amended per the Examiner's suggested title.

Along with this amendment, Applicants' have filed an Information Disclosure Statement ("IDS") and references to comply with 37 CFR 1.98(a)(2). Further, the listing of references in the specification (WO2007/0059230A1) at pages 7-8 has been included in the IDS.

The Examiner has rejected Claims 3-7 and 9-11 under 35 U.S.C. §103(a) as being unpatentable over Lidstrom *et al.* (J. Chem. Soc. Perkin Trans. 1, 1997) in view of Alberto *et al.* (J. Am. Chem. Soc., 2001).

According to the Examiner, Lidstrom *et al.* teaches in Scheme 1, the synthesis of [carbonyl-<sup>11</sup>C]ketones from [<sup>11</sup>C]carbon monoxide (see also line 1 of the Abstract). From this teaching the Examiner concludes that the process of preparing radiolabelled compounds by carbonylation with CO is known and points out that Lidstrom *et al.* fails to teach H<sub>3</sub>BCO as the donor of radiolabelled carbon monoxide in such a process.

The Examiner then cites Alberto *et al.* (page 3135, paragraph 4) as disclosing preparation of H<sub>3</sub>BCO from commercially available H<sub>3</sub>B-THF and reacting it *in situ* with an alcoholic solution of potassium hydroxide, K<sub>2</sub>[H<sub>3</sub>BCO<sub>2</sub>] could be produced at ambient pressures. According to the Examiner, this result was achieved by controlling the equilibrium of the two-way reaction between H<sub>3</sub>BCO and H<sub>3</sub>BTHF by selectively condensing the THF out of the reaction. The resultant K<sub>2</sub>[H<sub>3</sub>BCO<sub>2</sub>] was then used as an *in situ* source of CO in aqueous solution and as a reducing agent as pointed out by the Examiner. It was noted by the Examiner that H<sub>3</sub>BCO is an intermediate in this process and is formed prior to the K<sub>2</sub>[H<sub>3</sub>BCO<sub>2</sub>]. From this the Examiner concludes the process of preparing H<sub>3</sub>BCO is known. However, the Examiner has neglected to state that

Alberto does not disclose the use of radiolabelled  $\text{H}_3\text{BCO}$  as a donor of radiolabelled carbon monoxide, nor does this article even hint at such a use.

The Examiner goes on to state that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify Lidstrom's teaching in view of Alberto because it is well known in the art that radiolabelled  $\text{H}_3\text{BCO}$  can be used to release radiolabelled carbon monoxide in organic solvents, aqueous solvents and mixtures of organic and aqueous solvents in order to prepare radiolabelled compounds without the need for high pressure autoclaves or recirculation units. However, the Examiner has provided no evidence that the use of radiolabelled  $\text{H}_3\text{BCO}$  to release radiolabelled carbon monoxide was known in the art. There is certainly no basis in Lidstrom or Alberto for this assertion. Neither document states that  $\text{H}_3\text{BCO}$  can be used to release radiolabelled carbon monoxide. Lidstrom describes the radiolabelling of ketone-containing compounds without the use of  $\text{H}_3\text{BCO}$  and Alberto describes the carbonylation of metal complexes using non-radiolabelled  $\text{H}_3\text{BCO}$ .

It is the Examiner's position that one would have been motivated to make such a modification because existing methods for the trapping of  $[^{11}\text{C}]$ carbon monoxide for the production of radiolabelled compounds rely on the use of high pressure or recirculation of  $[^{11}\text{C}]$ carbon monoxide to maintain adequately high levels of  $[^{11}\text{C}]$ carbon monoxide in solution. This, according to the Examiner, would require the use of dedicated automated robotic systems for the handling of  $[^{11}\text{C}]$ carbon monoxide and specialized equipment. Borane carbonyl ( $\text{H}_3\text{BCO}$ ) is the immediate precursor to boranocarbonates, such as the potassium salt  $\text{K}_2[\text{H}_3\text{BCO}_2]$  which were reported to release CO in water at elevated temperatures. The drawbacks mentioned herein by the Examiner were all described in the specification of the current application as background to the current invention. Looking back on the problem and knowing the solution might make it seem obvious but at the time of filing the person skilled in the art of radiolabelling organic compounds (such as those used in PET) was motivated to invent some means for radiolabelling compounds with radioactive isotopes of atoms commonly occurring in such compounds, such as carbon or oxygen by

any suitable method. Incorporating the radiolabel into the actual structure of the compound is thought to affect that compound's behaviour less than having to "add-on" a radiolabel that does not form part of the structure under investigation. One of the main problems of using carbonylation to radiolabel compounds is that it is difficult to trap carbon monoxide in the small volume of organic solvent in which most of the precursors for the production of radiolabelled compounds are soluble. Small volumes of solvent are required because this allows easy isolation of the radiolabelled product by means of preparative HPLC and increases the concentration of the starting materials in the reaction mixture, thereby forcing the reaction in the desired direction (see page 1 of the instant specification). Therefore, the radiolabelling of compounds using radioactive carbon monoxide presented further obstacles in addition to those inherent to the preparation of radiolabelled carbon monoxide itself (e.g., high pressure, recirculation, specialized equipment, etc.).

With respect to the dependent claims of the present application, the Examiner points out that Alberto *et al.* (page 3135, col. 2, lines 10-14) teaches that the key to the preparation is the control of the equilibrium between  $\text{H}_3\text{BCO}$  and  $\text{H}_3\text{BCO-THF}$  and that THF (tetrahydrofuran) is the solvent for the Alberto reaction. The control of the equilibrium between  $\text{H}_3\text{BCO}$  and  $\text{H}_3\text{BCO-THF}$  is important to control release of the radiolabelled carbon monoxide and the choice of solvent optimizes the process. However, the inventive concept behind these dependent claims is still the application of  $\text{H}_3\text{BCO}$  as a donor of radiolabelled carbon monoxide for radiolabelling compounds.

The radiolabelling of organic compounds by carbonylation was acknowledged in the patent specification as being known at the time of filing (WO 2005/014479, page 2), as were the drawbacks:

"As an alternative method to using [ $^{11}\text{C}$ ]carbon dioxide for radiolabelling compounds, [ $^{11}\text{C}$ ]carbon monoxide may be used instead, as it is less prone to isotopic dilution with atmospheric carbon monoxide (0.1 ppm). Methods for the production of [ $^{11}\text{C}$ ]carbon monoxide by reducing [ $^{11}\text{C}$ ]carbon dioxide using reducing metals at high temperatures are well known (Gmelins 1972; Clark, *et al.*, 1975; Zeisler, *et al.*, 1997). Zinc and

molybdenum are the most widely used reducing agent for the [ $^{11}\text{C}$ ]carbon dioxide/carbon monoxide conversion.

However, it is difficult to trap  $^{11}\text{CO}$  in the small volume of organic solvent in which most of the precursors for the production of radiolabelled compounds are soluble. Small volumes of solvent are required because this allows easy isolation of the radiolabelled product by means of preparative HPLC and increases the concentration of the starting materials in the reaction mixture, thereby forcing the reaction in the desired direction. “

As the Examiner has noted in his report, Lidstrom *et al.*, does not teach the use of radiolabelled  $\text{H}_3\text{BCO}$  as the donor of radiolabelled carbon monoxide.

Alberto *et al.*, describes a process for preparing  $\text{H}_3\text{BCO}$  that allows the trapping of carbon monoxide. It is directed towards the production of a water-soluble, water-stable technetium carbonyl complex, not the production of radiolabelled carbon monoxide. Therefore, like Lidstrom *et al.*, the Alberto *et al.* reference does not teach the use of radiolabelled  $\text{H}_3\text{BCO}$  as the donor of radiolabelled carbon monoxide.

The Examiner suggests that “It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Lidstrom’s teaching in view of Alberto because it is well known in the art that radiolabelled  $\text{H}_3\text{BCO}$  can be used to release radiolabelled carbon monoxide in organic solvents....”. However, the Examiner does not give any basis for the assertion that radiolabelled  $\text{H}_3\text{BCO}$  was known to be useful for releasing radiolabelled carbon monoxide, nor has she given any weight to the fact that in radiolabelling compounds it is difficult to trap  $^{11}\text{CO}$  in the small volume of organic solvent in which most of the precursors for the production of radiolabelled compounds are soluble. The inventive concept at the heart of the invention is that using radiolabelled  $\text{H}_3\text{BCO}$  enables the preparation of radiolabelled carbon monoxide in a state that can be used to radiolabel organic compounds.

Indeed, this is a classic case of the invention looking obvious with the benefit of hindsight. Therefore, Claim 11 and its dependent claims are novel and inventive.

The Examiner has rejected Claims 2 and 8 under 35 U.S.C. §103(a) as being unpatentable over Lidstrom *et al.* in view of Alberto *et al.* and further in view of Carter *et al.* (J. Am. Chem. Soc., 1965). The Examiner points out that Claim 2 is drawn to the process of Claim 11 and additionally the radiolabelled H<sub>3</sub>BCO is prepared in the presence of a suitable base. With respect to Claim 8, the Examiner points out that it is drawn to the process of Claim 11 wherein the base is triethylamine, N-methyldibutylamine, M-methyl-2,2,6,6-tetramethylpiperidine, or N,N-di-isopropyl-ethylamine (DIPEA). According to the Examiner, Lidstrom *et al.* in view of Albert *et al.* teaches the process of Claim 11 as evidenced by the above-rejection. Carter *et al.* is cited by the Examiner for the preparation of H<sub>3</sub>BCO (page 2355, Col. 2, paragraph 1). The Examiner asserts that Carter *et al.* teaches a tri-methylamine base, a functional equivalent to triethylamine. From this the Examiner concludes that it would have been obvious to one of ordinary skill to prepare the radiolabelled H<sub>3</sub>BCO in such a base because it further enhances the products stability since H<sub>3</sub>BCO strongly dissociates at room temperature.

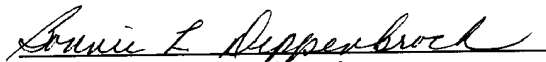
Applicants' argument set forth in response to the first 35 U.S.C. §103(a) rejection above are maintained. Again, the inventive concept at the heart of the invention is that radiolabelling the carbon or oxygen molecules in H<sub>3</sub>BCO enables the resulting radiolabelled carbon monoxide to be used to radiolabel organic compounds. The Examiner does not give any basis for the assertion that radiolabelled H<sub>3</sub>BCO was known to be useful for releasing radiolabelled carbon monoxide. For the present rejection, the Examiner asserts that Carter *et al.* teaches a tri-methylamine base and asserts that it is a functional equivalent to triethylamine. However, the Examiner does not assert, nor do any of the references cited by the Examiner show that tri-methylamine is a functional equivalent to triethylamine in Applicants' claimed process. Again, this is a case of the invention looking obvious only with the benefit of hindsight.

Therefore, Claim 11 and its dependent claims are novel and non-obvious in view of the references cited by the Examiner. Accordingly, it is respectfully

requested that all rejections of the claims be reconsidered and withdrawn and that the application as amended be allowed.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

  
Bonnie L. Deppenbrock  
Attorney for Applicant  
Registration No. 28,209

Date: 27 February 2008  
GlaxoSmithKline  
Corporate Intellectual Property  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709-3398  
Phone: 919-483-1577  
Facsimile: 919-483-7988